
Guidance for Industry

Regulatory Classification of Pharmaceutical Co-Crystals

DRAFT GUIDANCE

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I. INTRODUCTION

This draft guidance provides applicants of new drug applications (NDAs) and abbreviated new drug applications (ANDAs) with the Center for Drug Evaluation and Research's current thinking on the appropriate classification of co-crystal solid-state forms. This draft guidance also provides information about the data that should be submitted to support the appropriate classification of a co-crystal and the regulatory implications of the classification.

FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

II. BACKGROUND

Co-crystals are solids that are crystalline materials composed of two or more molecules in the same crystal lattice. Given this association of two or more molecules in the crystal lattice, it is useful to consider the association of components more generally. A drug product is a finished dosage form (e.g., tablet; capsule; or solution that contains an active pharmaceutical ingredient² (API) generally, but not necessarily, in association with inactive ingredients (excipients)).³ This association of the API with its excipient(s) is designed to achieve performance characteristics to ensure drug product stability, bioavailability, patient acceptance, and other quality characteristics.

However, this association of the API with its excipient(s) in the dosage form may vary considerably. At one extreme, this association of the API with its excipient(s) may be at a

¹ This guidance has been prepared by the Office of Pharmaceutical Science in the Center for Drug Evaluation and Research (CDER) at the Food and Drug Administration.

² For the purposes of this guidance, the term "active pharmaceutical ingredient" is synonymous with the term "drug substance" (as defined in 21 CFR 314.3).

³ See 21 CFR 210.3(b)(4).

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macromolecular level typical of a physical mixture, as in a tablet manufactured by dry compression of the API with various excipients. At another extreme, this association of the API with its excipient(s) may be at a molecular level, such as an API incorporated into a β -cyclodextrin excipient, in formulations designed for the purposes of enhancing drug bioavailability, enhancing stability, or masking taste. Another example where this association of the API with its excipient(s) exists at a molecular level may occur in the case of amorphous API-excipient dispersion, in formulations designed to enhance drug product bioavailability.

Traditionally, pharmaceutical solid-state forms of an API are grouped as either polymorphs or salts, and applicable regulatory schemes for these solid-state forms are well-defined. (See Glossary.) Co-crystals, however, are distinguishable from these traditional pharmaceutical solid-state forms. Unlike polymorphs, which generally speaking contain only the API within the crystal lattice,⁴ co-crystals are composed of an API with a neutral guest compound conformer in the crystal lattice. Similarly, unlike salts, where the components in the crystal lattice are in an ionized state, a co-crystal's components are in a neutral state and interact via nonionic interactions. At present no regulatory paradigm exists governing co-crystal forms.

Pharmaceutical co-crystals have opened the opportunity for engineering solid-state forms designed to have tailored properties to enhance drug product bioavailability⁵ and stability, as well as enhance processability of the solid material inputs in drug product manufacture.⁶ Pharmaceutical co-crystals are of interest because, unlike a salt form where the components in the crystal lattice are in an ionized state, the molecules in the co-crystal are in a neutral state and interact via nonionic interactions. Thus, pharmaceutical co-crystals offer the advantage of generating a diverse array of solid-state forms, even for APIs that lack ionizable functional groups needed for salt formation.

In response to the need for regulatory guidance, this draft guidance provides our current thinking on the appropriate classification of co-crystal solid-state forms, the data that should be submitted to support the classification, and the regulatory implications of such a classification.

III. DISCUSSION

Co-crystals are fully analogous to the instances where the association of the API and its excipient(s) interact at a molecular level, with the single exception being that in a co-crystal the molecular association occurs within the crystal lattice.

Therefore, co-crystals should be classified within the Agency's current regulatory framework as dissociable "API—excipient" molecular complexes (with the neutral guest compound being the excipient). Co-crystals within this broader category are uniquely defined by the fact that the molecular association of API and its excipient(s) occurs within the crystal lattice. In this

⁴ Polymorphic forms also may include solvate (or hydrate) forms that contain—in addition to the active ingredient—either stoichiometric or nonstoichiometric amounts of a solvent (or water) in the crystal lattice.

⁵ See for example, McNamara et al., "Use of a Glutaric Acid Cocrystal to Improve Oral Bioavailability of a Low Solubility API," *Pharmaceutical Research*, 23(8), 2006, pp. 1888-1897.

⁶ See for example, Trask et al., "Physical Stability Enhancement of Theophylline via Cocrystallization," *International Journal of Pharmaceutics*, 320, 2006, pp. 114-123.

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manner, an API that has been processed with a co-crystallizing excipient to generate an “API—excipient” co-crystal may be treated as a drug product intermediate.⁷

For applicable NDAs and ANDAs containing or claiming to contain a co-crystal form, the applicant should submit applicable data that accomplish the following:

- Determine whether, in the crystalline solid, the component API with the excipient compounds in the co-crystal exist in their neutral states and interact via nonionic interactions, as opposed to an ionic interaction, which would classify this crystalline solid as a salt form. Generally speaking, if the API and its excipient(s) have a ΔpK_a (pK_a (base) - pK_a (acid)) < 0 , there will be negligible proton transfer and the molecular complex will be a co-crystal. If the $\Delta pK_a > 3$, there will be complete proton transfer resulting in complete ionization and formation of a salt as opposed to a co-crystal. In instances where the $\Delta pK_a > 0$ and $\Delta pK_a < 3$, the extent of proton transfer and ionization is generally not predictable. In these cases, spectroscopic tools may be needed to probe the extent of proton transfer and ionization states to define where the solid-state form exists within the co-crystal/salt continuum.
- For pharmacological activity, ensure that the API dissociates from its excipient prior to reaching the site of action.

If these two pre-conditions are met in this manner, an API that has been processed with a co-crystallizing excipient to generate an “API—excipient” co-crystal should be treated as a drug product intermediate. As a drug product intermediate, the co-crystal is defined and controlled as part of the drug product in terms of, for example, formulation ingredients, solid state form, manufacturing process, and performance, but the API is still the same. Thus, co-crystal containing drug products (as defined in this guidance) will not be considered to contain new APIs, but rather to contain a specifically designed formulation component called a co-crystal drug product intermediate that is expected to contribute to improved drug product performance (e.g., solubility, dissolution).

⁷ For the purposes of this guidance, the term “drug product intermediate” is synonymous with the term “in process material” (as defined in 21 CFR 210.3(b)(9)).

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GLOSSARY

Co-crystals: Solids that are crystalline materials composed of two or more molecules in the same crystal lattice.

Polymorphs: Different crystalline forms of the same drug substance. This may include solvation or hydration products (also known as pseudopolymorphs) and amorphous forms. Per the current regulatory scheme, different polymorphic forms are considered the same active ingredients. (See Guidance for Industry: *ANDAs: Pharmaceutical Solid Polymorphism: Chemistry, Manufacturing, and Controls Information*, July 2007.)

Salts: Any of numerous compounds that result from replacement of part or all of the acid hydrogen of an acid by a metal or a radical acting like a metal: an ionic or electrovalent crystalline compound. Per the current regulatory scheme, different salt forms of the same active moiety are considered different active ingredients. (See 21 CFR 314.108 and 21 CFR 320.1(c).)